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Optimal Pulse Shapes and Durations for Cathodic Pacing of Excitable Tissues

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INTRODUCTION

Our purpose is to determine an optimal pulse shape and duration of cathodic current for pacing –just at its threshold- a given target element in an excitable tissue.

The target element may be a single cell (such as nerve fiber or skeletal muscle fiber) or a whole network of electrically coupled cells (such as the myocardium or visceral smooth muscle).

The response of the target element to the applied pulse is the all-or-none emergence of an action potential.

We use the criterion of least electric energy dissipated in the tissues to select an optimal pulse shape amongst the different (just-threshold) cathodic ones of a given duration.

We calculate the corresponding minimum of dissipated electric energy and then we study its variation with the duration of the pulse.

METHODS

From a phenomenological standpoint the excitation process of a given target element in an electrode-tissues system may be described by an "excitation functional" (1), (2).

For cathodic make excitation with a just-threshold pulse i(t) of duration t_P, the criterion of the *excitation functional* (in the linear approximation) reduces to the following equality :

$$\int_0^{t_P} g\left(t_P - t\right)\cdot i\left(t\right)dt = q_u \qquad [1]$$

Here q_u is a certain threshold charge and g(t) is an impulsive response function studied elsewhere (2), (3) , (4) (Figure 1).

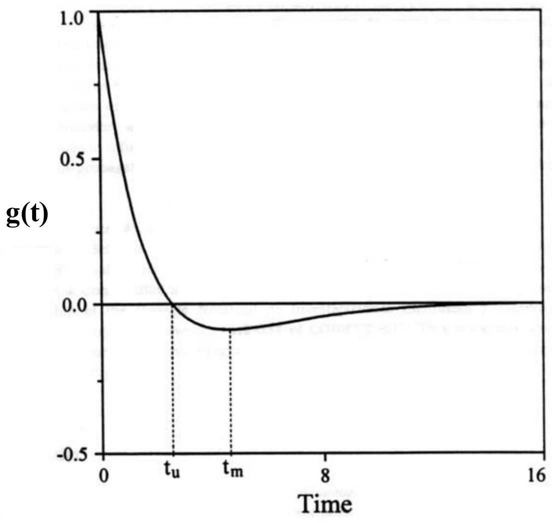

Fig. 1: The impulsive response function of an "excitation functional".

This function is positive between t=0 and $t=t_u$, where t_u is the useful time up to the rheobase (defined using strength-duration curves) (5) (Figure 2).

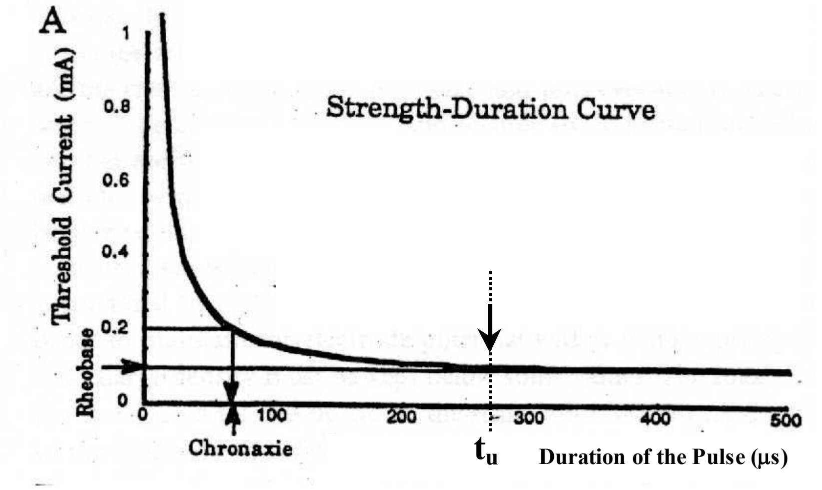

Fig. 2: The useful time up to the rheobase t_u

Furthermore, to apply [1] as a starting point, we suppose that at the beginning of the current pulse the excitable membranes of the target element are at their rest state.
Applying the Cauchy-Bunyakowsky-Schwarz inequality (6)

$$\left| \int_0^{t_P} g(t_P - t) \cdot i(t)\, dt \right|^2 \le \int_0^{t_P} g^2(t)\, dt \cdot \int_0^{t_P} i^2(t)\, dt \qquad [2]$$

The inequality is an equality if and only if:

$$i(t) = K\, g(t_P - t) \qquad [3]$$

Now from [1], for a just-threshold pulse the left-hand member of [2] must be equal to the constant: q_u^2.

Then, for a just-threshold current pulse:

$$\int_0^{t_P} i^2(t)\,dt \geq \frac{q_u^2}{\int_0^{t_P} g^2(t)\,dt} \qquad [4]$$

But if the biological tissues can be represented by an ohmic load of resistance R_T, the dissipated electric energy per pulse, can be calculated as:

$$R_T \int_0^{t_P} i^2(t)\,dt \qquad [5]$$

RESULTS

For a just-threshold pulse this energy will be a minimum if inequality [2] is an equality, that is if i(t) verifies equation [3]. Substituting [3] into [1], we determine the constant of proportionality K. After that, from [3] we obtain the optimal pulse shape, for cathodic make excitation, and for a given duration t_P between 0 and t_u:

$$i(t) = \frac{q_u^2}{\int_0^{t_P} g^2(t)\,dt} \cdot g(t_P - t) \qquad [6]$$

From [4] and [5] it follows that the energy dissipated by an optimal pulse of duration t_P is given by

$$\frac{R_T \cdot q_u^2}{\int_0^{t_P} g^2(t)\,dt} \qquad [7]$$

To use formula [6] for the optimal pulse shape and the expression [7] for the minimum of electric energy dissipated in

the tissues, both q_u and g(t) must be known. In principle, they can be determined from the measurement of the corresponding strength-duration curves for each target element in its electrode-tissue system. To see how this can be done, let us consider a rectangular pulse of cathodic current, of amplitude i_0 and duration t_P. From the criterion given by equation [1], the pulse will be just threshold if and only if:

$$i_0 = i_0(t_P) = \frac{q_u}{\int\limits_0^{t_P} g(t)\,dt} \qquad [8]$$

In this formula, t_P is between 0 and t_u. Now, if $i_0=i_0(t_P)$ is known (measuring the corresponding strength-duration curve), from equation [8] it follows that

$$q_u = \lim_{t_p \to +\infty} \left(t_P \cdot i_0(t_P)\right) \qquad [9]$$

$$g(t_P) = \frac{d}{dt_P}\left[\frac{q_u}{i_0(t_P)}\right] \qquad [10]$$

for each t_P between 0 and t_u.

In practice equation [10] shouldn't be used to calculate g(t) form experimental data.
The corresponding numerical problem has a very bad condition number, so that there is too much uncertainty in the estimation of g(t).
To bypass this problem, we can use a closed form analytical formula with a few adjustable parameters to represent g(t), substitute it in formula [8] and adjust the parameters to an experimental strength-duration curve.
The required formulae can be obtained from suitable mathematical models of threshold dynamics for fibers (4), (7) or networks of electrically coupled cells (2), (3) stimulated by external electrodes.
Also, it is possible to directly introduce the linear version of the excitation functional for a cathodic pulse (Equation [1]) (1), (2), and then to use a descriptive mathematical model for g(t), with suitable free parameters.

DISCUSSION

From [6] the optimal pulse shape of duration t_P can be determined.
As g(t) is decreasing (between 0 and t_m , see Figure 1) and convex (because $\frac{d^2}{dt^2} g(t) > 0$), the optimal pulse shape is increasing and convex.
From [7] it follows that as t_P increases, the minimum dissipated energy per pulse decreases at its turn and reaches its minimum when $t_P=t_u$.
The experiments show that the parameters of the strength-duration curves, and therefore q_u and g(t), depend not only on the excitability properties of the membranes of the target element, but also depend on certain geometric and bioelectric parameters of the system formed by the electrodes, the tissues, and the target element within the tissues.

For example, if the target element is a fiber, they depend on the radius of the fiber. Besides, they depend on the distance between the cathode and the target element, and of the size and shape of the active electrode if it is located close enough to the target element.
Furthermore, the dissipated energy per pulse is proportional to R_T.
But R_T usually depends on the size and shape of the cathode (we suppose monopolar stimulation) and it is very sensitive to conductivity variations in the tissues located near the active electrode (such as the ones related with inflammatory reactions to implant electrodes).
Therefore, the optimal pulse shape for a given duration can be modified, in the same electrode-tissues-target element system, due to the variation of the parameters of the system.
A new digital stimulator for threshold research and synthesis of optimal pulse shapes was developed, considering these results (8), (9).

CONCLUSIONS

(a) For a given duration, and a just-threshold pulse, the optimal shape is given by equation [6].

(b) The energy dissipated by an optimal pulse shape decreases as the pulse duration increases.

(c) Besides being increasing and convex, there doesn’t seem to be other general properties of the optimal pulse shape. For each target element in its corresponding electrode-tissues system, the optimal pulse shape should be determined from strength-duration measurements.

(d) In the case of implant electrodes during chronic pacing, the variations in the parameters of the strength-duration curves for the same electrode-tissues-target element system could be so significant that its influence on the optimal pulse shape can’t be neglected (for example, when the distance between the electrode and the target element varies).

(e) The present approach, related with the theory of matched filters in electric engineering, is simple and straightforward. But it is suitable only for the criterion of minimum dissipated electric energy per pulse, in ohmic tissues. In other cases, the more powerful methods of functional analysis must be used (1).

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OPTIMAL PULSE SHAPES FOR PACING EXCITABLE TISSUES

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Introduction: The posed problem (to find an optimal cathodic pulse shape (PS) for chronic autonomous pacing at threshold a given excitable tissue) can be approached from two standpoints: minimizing electric energy dissipation in tissues or minimizing battery drainage.

Materials and Methods: An **dissipation functional** (EF) is introduced and defined as the temporal convolution of an impulse response function (IRF) with a cathodic PS. Then a given cathodic PS is just threshold if and only if the value of the EF equals a threshold charge (Th. Ch.). Both, IRF and Th. Ch can be experimentally determined from measured strength-duration curves and some additional information. Electric energy dissipated in the tissues (ohmic resistance) and in the whole system (in series combination of ohmic resistance of electrode's cable, tissues resistance and polarization resistance of electrode-tissue interface - given by an Abel's operator) is described by the corresponding **dissipation functional** (DF) of the PS.

Results: The variational problem of finding the cathodic PS that minimizes one or another DF meanwhile the EF remains at its threshold value (or fixed over it) is solved by methods of functional analysis. The obtained PS is a monotonic increasing function of time, in good accord with known experimental facts for cardiac pacing. Bioelectric properties of tissue's target region -among other variables- determine optimal PS.

Conclusions: Optimal cathodic PS is a property of the electrode-tissue system. For the same electrode-tissue system, it can vary during chronic pacing. But if wished, optimal PS can be found from measurements with rectangular pulses.

Keywords: autonomous chronic pacing at threshold of an excitable tissue, optimal cathodic pulse shapes, autonomous chronic pacing of the heart, electric energy dissipation in tissues, battery drainage, ohmic resistance of electrode's cable, tissues resistance, polarization resistance of electrode-tissue interface, dissipation functional, excitation functional, restricted variational problem, functional analysis methods

(A) Introduction

During the first stages in design and construction of implantable cardiac pacing systems, the problem of identifying pulse shapes and durations that minimize the charge drainage from the batteries was posed (Angelakos and Torres, 1964; Roy and Wehnert, 1971; Fiandra, 1985, chapter 7).

Now, this is not a pressing problem as it was before, but minimizing the energy dissipated in the tissues in conditions of acute and chronic stimulation continues to be a goal to achieve.

The problem to be solved here, from a physical-mathematical point of view, is to find an optimum cathodic pulse shape for chronic autonomous pacing at threshold a given target element in an excitable tissue.
The target element may be a nerve fiber or skeletal muscle fiber (Rattay, 1990) or an electrical syncytium such as myocardium or electrically coupled visceral smooth muscle. The response of the target element to the applied pulse is the all-or- none emergence of an action potential.

In principle the optimization problem can be approached from two standpoints: minimizing electric energy dissipation in tissues or minimizing battery drainage. In this research, to simplify the mathematical analysis, we work with a linear model of the electrode-tissue system relating the voltage between an active electrode (cathode) and an indifferent one (the anode), with the electric current injected in the biological tissues through the stimulating system.

From a phenomenological standpoint the excitation process of a given target element in an electrode-tissues system may be described by an excitation functional (Fiandra, 1985, chapter 8; Suarez-Antola, 1994). In this research, also to simplify the mathematical analysis, we use a linear approximation to the excitation functional.

(B) Materials and Methods

To solve the optimum problem, we introduce two functionals: an **excitation functional** $\psi[i]$ and an **energy dissipation functional** $\varphi[i]$.

The excitation functional: For a cathodic make excitation with a pulse $i(t)$ of duration t_p, the excitation functional gives a necessary and sufficient condition to identify a just-threshold cathodic pulse.

This excitation condition, **in the linear approximation**, reduces to the following equality, where Q_u represents a certain threshold charge, and $G(t)$ is an **impulse response function**:

$$\psi[i] = \langle g, i \rangle = \int_0^{t_P} G(t_P - t) \cdot i(t) \cdot dt = Q_u \qquad (1)$$

Here $g(t) = G(t_p - t)$ and $\langle g, f \rangle = \int_0^{t_p} g(t) \cdot f(t) \cdot dt$ is an internal product in the space $C[0, t_p]$ of continuous real functions in the interval $[0, t_p]$.

The impulse response function $G(t)$ is positive between $t = 0$ and $t = t_u$ where t_u is the so-called useful time up to the rheobase (see Figure 1)

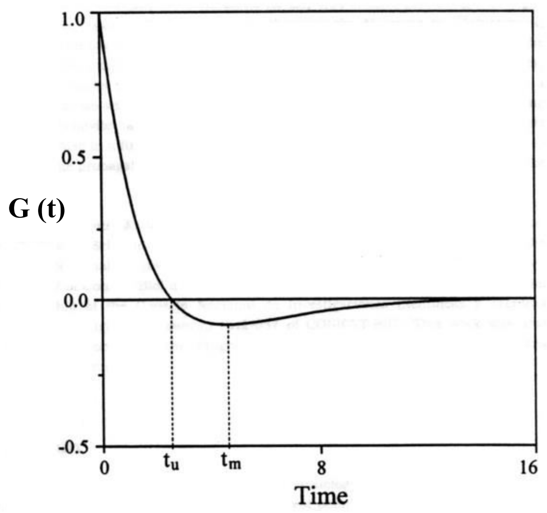

Figure 1: The impulsive response function of a linear approximation to the excitation functional (Suarez-Antola, 1994).

To apply Equation (1) as a starting point, we suppose that at the beginning of the current pulse the excitable membranes of the target element are at their rest state.
Both, the impulse response function, and the threshold charge can be experimentally determined from measured strength-duration curves and some additional information.

The energy dissipation functional: The energy dissipation functional $\varphi[i]$ can be obtained from the power dissipated by a cathodic pulse in the active electrode interface, in the electrode leads and, in the tissues, neglecting the counter-electrode effects. If $V(t)$ is the voltage between the input end of the active electrode lead and the indifferent electrode, then we put: $\varphi[i]=\int_0^{t_p} V(t)\cdot i(t)\cdot dt$ In the linear approximation (Suarez-Antola, 1994):

$$V(t)=R_p\cdot i(t)+\int_0^t K(t-u)\cdot i(u)\cdot du \tag{2}$$

The ohmic resistance $R_p=R_c+R_T$ is the sum of an ohmic lead resistance R_c and the tissues resistance R_T. This last one, in the conditions of electric stimulation can be taken as ohmic also (Schaldach y Furman, 1975; Fiandra, 1985; Rattay, 1990).

The polarization resistance of electrode-tissue interface is described, in the linear approximation, by the convolution term $\int_0^t K(t-u)\cdot i(u)\cdot du$.

Then, for a cathodic make excitation with a pulse $i(t)$ of duration t_p the energy dissipation functional $\varphi[i]$ may be written, in the linear approximation:

$$\varphi[i] = R_p \cdot \int_0^{t_p} i^2(t) \cdot dt + \int_0^{t_p} i(t) \cdot \left(\int_o^t K(t-u) \cdot i(u) \cdot du \right) \cdot dt$$

In inner product notation we have:

$$\varphi[i] = R_p \cdot \langle i, i \rangle + \left\langle \hat{K} i, i \right\rangle \qquad (3)$$

Here, by definition, the linear operator $\hat{K}$ verifies:

$$\hat{K}\, i(t) = \int_o^t K(t-u) \cdot i(u) \cdot du \qquad (4)$$

According to De Boer, R. and A. van Oosterom (1978) the kernel of this operator is given by $K(t) = K_0 \cdot \left(\frac{t}{T_0} \right)^m$, where K_0, T_0 and m are positive parameters ($0 < m < 1$). It is an Abel's operator. The properties of the interface between the active electrode and the tissues can vary during chronic stimulation (Schaldach, M. y S. Furman, 1975; Irnich, 1985; Rattay, 1990) so we can expect some variation in the above introduced parameters.

The energy dissipation functional $\varphi[i]$ **is positive definite** because both dissipation terms, $R_p \cdot \langle i, i \rangle$ and $\left\langle \hat{K} i, i \right\rangle$, are strictly positive if the cathodic current pulse is not identically zero.

The optimum problem: To find a just-threshold cathodic pulse shape $i_0(t)$, continuous in the time interval $\lfloor 0, t_p \rfloor$, such that:

(I) $\psi[i_0] = Q_u$ (just-threshold condition) while

(II) $\varphi[i_0] < \varphi[i_0 + \delta i]$ for every other pulse shape $i_0 + \delta i$ such that $\psi[i_0 + \delta i] = Q_u$ (so $i_0 + \delta i$ is any other just threshold pulse shape).

Notice that, due to the linearity of the excitation functional, from $\psi[i_0] = Q_u$ and $\psi[i_0 + \delta i] = Q_u$ it follows that for every variation δi :

$$\psi[\delta i] = 0 \qquad (5)$$

From Equation (3) we derive:

$$\varphi[i_0 + \delta i] - \varphi[i_0] = 2 \cdot R_p \cdot \langle i_0, \delta i \rangle + \left\langle \hat{K} i_0, \delta i \right\rangle + \left\langle i_0, \hat{K} \delta i \right\rangle + o(\delta i) \qquad (6)$$

Here $o(\delta i) = R_p \cdot \langle \delta i, \delta i \rangle + \left\langle \delta i, \hat{K} \delta i \right\rangle$ **is always positive** if δi is not identically zero.

So, if we find a current just threshold pulse $i_0(t)$ such that for every perturbation δi that verifies $\psi[\delta i] = 0$, we have $2 \cdot R_p \cdot \langle i_0, \delta i \rangle + \left\langle \hat{K} i_0, \delta i \right\rangle + \left\langle i_0, \hat{K} \delta i \right\rangle = 0$, then $i_0(t)$ will be an optimum pulse shape.

Now, the continuous operator $\hat{K}$ has an adjoint operator $\hat{K}^*$ (Cotlar and Cignoli, 1974; Griffel, 1983).

As consequence: $$\left\langle i_0, \hat{K}\delta i \right\rangle = \left\langle \hat{K}^* i_0, \delta i \right\rangle \tag{7}$$

Taking (7) into account we derive: $2 \cdot R_p \cdot \langle i_0, \delta i \rangle + \left\langle \hat{K} i_0, \delta i \right\rangle + \left\langle i_0, \hat{K}\delta i \right\rangle = 2 \cdot R_p \cdot \left\langle \hat{A} i_0, \delta i \right\rangle$

Here, by definition, the operator $\hat{A}$ verifies:

$$\hat{A} = \hat{I} + \frac{1}{2 \cdot R_p} \cdot \left(\hat{K} + \hat{K}^*\right) \tag{8}$$

As usual, $\hat{I}$ is the identity operator.

Considering that, from Equation (1) it follows $\psi[\delta i] = \langle g, \delta i \rangle$ and considering Equation (8), the optimum problem can be recast as follows:

To find $i_0(t)$ such that: $\left\langle \hat{A} i_0, \delta i \right\rangle = 0$ for every perturbation that verifies $\langle g, \delta i \rangle = 0$

(C) Results and Conclusions

If two linear functionals like $\left\langle \hat{A} i_0, \delta i \right\rangle$ and $\langle g, \delta i \rangle$ have the same null set, the functions $\hat{A} i_0(t)$ and $g(t)$ must be proportional (Cotlar and Cignoli, 1974):

$$\hat{A} i_0(t) = \lambda \cdot g(t) \tag{9}$$

Equation (9) is a convolutive Volterra's integral equation of the second kind, so it always has a unique solution for every continuous function $g(t)$ in $\left[0, t_p\right]$ (Moissiiewitsh, 1977).

If $\hat{A}^{-1}$ is the inverse operator: $$i_0(t) = \lambda \cdot \hat{A}^{-1} g(t) \tag{10}$$

Now, as $i_0(t)$ must be a just-threshold pulse:

$$\psi[i_0] = \langle g, i_o \rangle = Q_u \tag{11}$$

Substituting (10) in (11) we obtain:

$$i_0 = \frac{Q_0}{\left\langle g, \hat{A}^{-1} g \right\rangle} \cdot \hat{A}^{-1} g \tag{12}$$

This is the optimum threshold current pulse that we were searching.

It can be shown (De Boer and van Oosterom, 1978) that the effect of the polarization of the interface can be often neglected. In this case the shape of the optimum pulse is determined mainly by the function $g(t) = G(t_p - t)$.

As will be studied elsewhere, known experimental results (Angelakos, E. and J. Torres, 1964; Roy and Wehnert, 1971; Klafter, R. and L. Hrieben, 1976) agree with this prediction.

The experiments show that the parameters of the strength-duration curves, and therefore the threshold charge and the impulse response function depend, besides the threshold properties of the membranes of the target element, of certain geometric and bioelectric parameters of the system formed by the electrodes, the tissues, and the target element within the biological tissues. For example, they depend on the distance between the cathode and the target element, and of the size and shape of the active electrode if it is located close enough to the target element.
The ohmic term in the dissipated energy per pulse is proportional to $R_p = R_c + R_T$.
But R_T usually depends on the size and shape of the cathode (we suppose monopolar stimulation) and it is very sensitive to conductivity variations in the tissues located near the active electrode, such as the ones related with inflammatory reactions to implant electrodes (Fiandra, 1985).
Consequently, the optimal pulse shape for a given duration can be modified, in the same electrode-tissues-target element system, due to the variation of the parameters of the system.

To end:

(a) Optimal pulse shape is a property of the electrode-tissue-target element system. For the same electrode-tissue-target element system, it can vary during chronic stimulation of myocardium, nerve, or skeletal muscle.

(b) In principle, optimal cathodic pulse shape could be found at each moment from measurements of the strength-duration curves and from a characterization of the polarization resistance of the active electrode interface, employing rectangular pulses of controlled electric current. For a given duration, and a just-threshold pulse, the optimal shape is given by equation (12).

(c) In the case of implant electrodes during chronic pacing, the variations in the parameters of the strength-duration curves for the same electrode-tissues-target element system could be so significant that its influence on the optimal pulse shape can't be neglected (for example, when the distance between the electrode and the target element varies).

(d) A nonlinear analysis of the optimum cathodic pulse shape remains to be done.

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Contributions to the study of optimal biphasic pulse shapes for functional electric stimulation: An analytical approach using the "excitation functional".

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Abstract—**An analytical approach to threshold problems in functional electric stimulation and pacing is proposed, framed in the concept of *excitation functional*. This *functional* can be applied to nerve, muscle, and myocardium stimulation by external electrodes. An optimal shape for a biphasic pulse is found, using the criteria of minimum energy dissipated in biological tissues and total charge compensation between the excitatory cathodic and the compensatory anodic phases. The method can be further developed and applied to other threshold problems in functional electric stimulation and pacing.**

I. INTRODUCTION

ELECTRICAL stimulation of excitable biological tissues by working electrodes, located near the target elements in which action potentials must be produced, pose several interesting problems from an engineering standpoint.

Reference [1] reviews the state of the art in relation with the design of efficacious and safe protocols for functional electric stimulation, both from an electrophysiological and clinical point of views, considering the electrochemical aspects of charge injection and the mechanism of damage to tissues and electrodes. Biphasic current pulses are needed. Usually, a cathodic half pulse of rectangular shape is followed by an anodic one (rectangular or exponentially decreasing), often after a short delay time. The charge compensation thus obtained at the electrode-electrolyte interface, allows pacing the target tissue without a significant damage to the biological tissues located near the working electrode or the counter electrode (necessary to close the circuit) [1], [2].

The purpose of the present paper is to contribute to the design of stimulation protocols that, besides being efficacious and safe, may be considered as optimal from an engineering point of view. Minimum charge drainage and transfer, minimum energy dissipation in biological tissues or in the whole working electrode-tissues-counter electrode system, as well as optimal durations of the cathodic and anodic components of the biphasic pulses and of the delay time between the cathodic and the anodic parts are some reasonable design aims that may be imposed for *just threshold* electric current pulses [3]. So, a *threshold condition* that allows us to classify biphasic pulses as below, above, or just at threshold is needed to discuss and solve optimization problems. After that, a *safety factor* must be introduced to apply the obtained results in clinical practice.

Thresholds for different pulse shapes can be measured in true electrophysiological experiments in realistic settings. Complementary information may be produced by digital simulation using standard computing codes that allows us to consider the effect of an external working electrode in a target fibre or syncytium with varying geometries. But as our intention is to develop an analytical approach to optimization problems, we will use the *excitation functional* as main mathematical tool. In a previous work a simplified version of the excitation functional, (taking into account membrane accommodation processes but assuming that activation processes were instantaneously relaxed to equilibrium with membrane voltage), was used to study just threshold *monophasic cathodic* pulse shapes that minimize the energy dissipated in biological tissues [4]. As a more complex and realistic example of the proposed method, we discuss cathodic make excitation with *biphasic* pulses in which the anodic pulse achieves total charge compensation. We perform this task using a theoretical framework grounded in a more complete version of the functional, that also allows to study both *one-phase* and *biphasic anode break excitation*. The idea of an excitation functional is implicit in the early classical *one and two factor models of excitation* (due to Monnier, Hill, Rashevski, and generalized later by FitzHugh, although only for uniformly polarized membranes) [5] [6]. However, it seems that the first explicit proposal of the functional was done in a contribution to the 1994-World Congress in Medical Physics and Biomedical Engineering [3].

Here we postulate the functional and its main properties. But it is possible to give to it a rigorous biophysical foundation grounded in equations of membrane dynamics and the modern tools of nonlinear science [7]-[9].

II. THE "EXCITATION FUNCTIONAL"

A. *Definition of the excitation functional*

In the following we consider in general the electric stimulation of nerve and muscular fibres, as well as myocardium and other electric syncytia.

For each electrodes-tissues-target element system, we introduce a *dimensionless impulsive response function* $G(t)$ that characterizes an *equivalent charge transfer response* to an applied electric current pulse $i(t)$. A formula for $G(t)$ and its description will be given in the next section.

From now on, *cathodic pulses will be taken as positive functions of time, and anodic pulses as negative time functions.*

If the excitable membranes of the target element are in their rest state when $t \le 0$ and the pulse begins when $t = 0$, let us construct the following *equivalent charge*:

$$q_e(t) = \int_0^t G(t-u).i(u).du \qquad (1)$$

Now, let us consider a pulse $i(t)$ and let us take the maximum value of $q_e(t)$ for $0 \le t$. This procedure makes a correspondence between each function $i(t)$ and a real number: this defines a *functional* $F[i]$.

There is a positive *threshold value* $q_{e,T}$ such that if a pulse $i(t)$ verifies $F[i] < q_{e,T}$ it is below threshold (the action potential doesn't emerge in the target tissue), if $F[i] > q_{e,T}$ it is above threshold (an action potential emerges in the target tissue), and if $F[i] = q_{e,T}$ it is a just threshold pulse.

While the convolution that defines $q_e(t)$ is linear operation, the excitation functional $F[i]$ is a *nonlinear* correspondence between functions and numbers, due to the appearance of the maximum of $q_e(t)$ in its definition.

B. *The impulsive response functions.*

Then the impulsive response is:

$$G(t) = \frac{\lambda_3}{\lambda_3 - (\lambda_1 + \lambda_2)} . \left\{ \frac{\lambda_2}{\lambda_2 - \lambda_1} \left(e^{-\lambda_2 . t} - e^{-\lambda_3 . t} \right) - \frac{\lambda_1}{\lambda_2 - \lambda_1} \left(e^{-\lambda_1 . t} - e^{-\lambda_3 . t} \right) \right\} . H(t) \qquad (2)$$

Here $\lambda_1, \lambda_2, \lambda_3$ are kinetic parameters of the electrode-tissues-target element system. (With the opposite sign convention for electric current pulses, $-G(t)$ must be used instead of $G(t)$). The parameter λ_3 is related with the activation processes in the excitable membranes, and it is at least one order of magnitude greater than both, λ_2 and λ_1. When the distance between the electrode and the target tissue is great enough in comparison with the space constant of the tissue, and the accommodation processes are fast enough, λ_1 and λ_2 are complex conjugate numbers. If not, they are real numbers and λ_1 always smaller than λ_2. Heaviside's unit step function $H(t)$ is equal to 0 if $t < 0$ and to 1 if $t \ge 0$.

Figure 1 shows a typical impulsive response function, when both parameters λ_1 and λ_2 are real numbers.

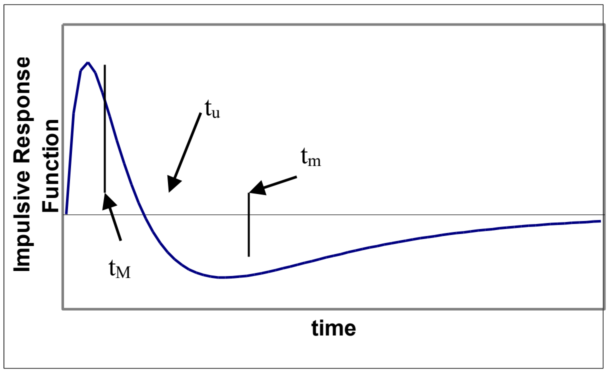

Fig. 1. Sketch of an Impulsive Response Function.

$G(t)$ is positive between 0 and t_u, and negative after. The growing of $G(t)$, from $G(0) = 0$ up to $G(t_M) = 1$, is due to the activation processes in the excitable membranes of the target tissue. The negative part after t_u is due to the accommodation processes in those membranes.

Considering the difference in the time scales of activation processes, membrane time constant and accommodation processes, the following approximate formulae are derived from (2):

$$t_M \approx \frac{1}{\lambda_3}\ln\frac{\lambda_3}{(\lambda_1+\lambda_2)} \tag{3}$$

$$t_u \approx \frac{1}{(\lambda_2-\lambda_1)}\ln\frac{\lambda_2}{\lambda_1} \tag{4}$$

$$t_m \approx 2.t_u \tag{5}$$

If the activation process is instantaneous: $\lambda_3 = \infty$ Then formula (2) may be simplified:

$$G(t) = \left\{\frac{\lambda_2}{\lambda_2-\lambda_1}\left(e^{-\lambda_2.t}\right) - \frac{\lambda_1}{\lambda_2-\lambda_1}\left(e^{-\lambda_1.t}\right)\right\}.H(t) \tag{6}$$

When the accommodation processes are slow enough, λ_1 is at least one order of magnitude smaller than λ_2, and it is possible to make the approximation $\lambda_1 = 0$. Then:

$$G(t) = e^{-\lambda_2.t}.H(t) \tag{7}$$

It is possible to express λ_2 as a well-defined function of the membrane parameters of the target element (including time and space constants), distance between the working electrode and the target tissue, and electrode's radius [7]-[9].

Recent applications of (7) to the study of time constants for cathodic make stimulation of nerve and muscle fibers as well as electric syncytia like myocardium, may be found in [10] [11].

C. Application of the excitation functional to a cathodic pulse of constant amplitude: strength-duration curves for cathodic make excitation with monophasic current pulses

Let us consider a rectangular pulse of duration t_c and positive amplitude I_c:

$$i(t) = I_c.[H(t) - H(t-t_c)] \tag{8}$$

From (2) we obtain:

If $t \le t_c$ then:

$$q_{e,c}(t) = I_c\int_0^t G(u).du \tag{9a}$$

So:

$$\frac{dq_{e,c}(t)}{dt} = I_c.G(t) \tag{9b}$$

Is positive if $0 < t < t_u$ and it is negative if $t > t_u$ (Fig.1).

If $t_c \le t$ then:

$$q_{e,c}(t) = I_c\int_{t-t_c}^{t} G(u).du \tag{10a}$$

So:

$$\frac{dq_{e,c}(t)}{dt} = I_c.(G(t) - G(t-t_c)) \tag{10b}$$

Is positive if $G(t) > G(t-t_c)$, it is zero in case of equality and negative if the inequality is reversed.

For fixed pulse amplitudes, the maximum value of $q_{e,c}(t)$ is attained when $t_c = t_u$. The minimum threshold amplitude (*rheobase*) $I_{c,Rb}$ then verifies:

$$I_{c,Rb}\cdot\int_0^{t_u} G(u).du = q_{e,T} \tag{11}$$

When $t_c < t_u$ the maximum of $q_{e,c}(t)$ is attained *after* the end of the pulse, for an instant $\tilde{t}$ such that (Fig2):

$$G(\tilde{t}) = G(\tilde{t} - t_c) \tag{12}$$

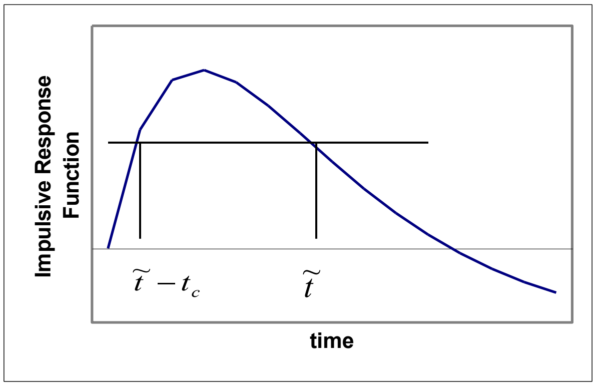

Fig. 2 Sketch of the graphical meaning of equation (12).

This is due to the increasing (between 0 and t_M) and decreasing (after t_M) phases of $G(t)$

If $t_M = 0$ *(instantaneous activation of the membrane) the increasing phase disappears and the maximum of* $q_{e,c}(t)$ *is attained always at the end of the pulse.*

Solving (12) with (2), and considering the different time scales to make some approximations:

$$\tilde{t} - t_c = \varepsilon_c(t_c) \approx \frac{1}{\lambda_3}\ln\left[\frac{(\lambda_2-\lambda_1).\left(1-e^{-\lambda_3.t}\right)}{\lambda_2.\left(1-e^{-\lambda_2.t}\right) - \lambda_1.\left(1-e^{-\lambda_1.t}\right)}\right] \tag{13}$$

The function $\varepsilon_c(t_c)$ decreases from t_M to 0 when t_c increases from: $t_c = 0$ to $t_c = t_u$

The excitation functional gives the following analytical formula for pulses of duration t_c and threshold amplitudes $I_{c,T}$ (*strength-duration curve*):

$$I_{c,T}(t_c) = \frac{q_{e,T}}{\int_{\varepsilon_c(t_c)}^{t_c+\varepsilon_c(t_c)} G(u).du}. \tag{14}$$

The limit of $t_c.I_{c,T}(t_c)$ when t_c tends to 0 is the so called *cathodic limit threshold charge*: $Q_{c,T,0}$ It is experimentally determined from the measured strength-duration curves. From (14) we find that

$$q_{e,c} = Q_{c,T,0} \qquad (15)$$

From (11) we obtain this formula for the cathodic time constant of the system: $t_{c,S} = \dfrac{Q_{c,T,0}}{I_{c,Rb}} = \int_0^{t_u} G(u).du$

(16)

D. Thresholds for rectangular biphasic pulses with delay between the cathodic and the anodic parts

Let us consider a biphasic pulse $i_b(t)$ formed by the superposition of two rectangular component pulses. The first one, $i_c(t)$ cathodic, has positive amplitude I_c and duration t_c. The second one, $i_a(t)$ anodic, has negative amplitude I_a and duration t_a. There is a time delay t_d between them. The duration of the biphasic pulse is $t_c + t_d + t_a = t_p$

The equivalent charge is the sum of two contributions:

$$q_e(t) = q_{e,c}(t) + q_{e,a}(t)$$

(17)

$$q_{e,c}(t) = \int_0^t G(t-u).i_c(u).du \qquad (18)$$

$$q_{e,a}(t) = \int_0^t G(t-u).i_a(u).du \qquad (19)$$

$q_{e,a}(t) = 0$ if $0 \le t < t_c + t_d$, so that in this time interval $q_e(t) = q_{e,c}(t)$

After that, the negative anodic equivalent charge $q_{e,a}(t)$ adds to the positive equivalent charge and tends to diminish $q_e(t)$ If $t_d < \varepsilon_c(t_c)$, the maximum of $q_e(t)$ will be less than $q_{e,c}(t_c + \varepsilon_c(t_c))$ and to just reach $q_{e,T}$ the amplitude of the cathodic pulse needs to be higher, *raising the threshold*.

If $t_d \ge \varepsilon_c(t_c)$ this effect disappears: the anodic compensating pulse doesn't interfere with the threshold of the excitatory cathodic part.

III. BIPHASIC PULSES WITH CHARGE COMPENSATION AND LEAST ENERGY DISSIPATION IN BIOLOGICAL TISSUES

Here we are going to apply the results obtained in Part II to an optimization problem: find the shape or shapes $i_b(t) = i_c(t) + i_a(t)$ of *just threshold biphasic pulses* that produce a *minimum of dissipated energy in ohmic biological tissues. In quantitative terms, we seek to make the quadratic functional:*

$$\int_0^{t_p} i_b{}^2(t).dt \qquad (20)$$

a minimum maintaining the excitation functional at its threshold value:

$$F[i_b] = q_{e,T} \qquad (21)$$

Note that $\displaystyle\int_0^{t_p} i_b{}^2(t).dt = \int_0^{t_c} i^2{}_c(t).dt + \int_{t_c+t_d}^{t_c+t_d+t_a} i^2{}_a(t).dt \qquad (22)$

Besides the just threshold condition (21), we introduce *two further restrictions*.

The first one is that t_d should be greater than t_M so that we could expect that the anodic part doesn't interfere with the threshold of the excitatory cathodic part, even if this last one doesn't have a rectangular shape. In this case: $F[i_b] = F[i_c]$ Then the threshold condition must be applied only to the cathodic part of the pulse.

The second restriction is *complete charge compensation*: if $i_{c,T}(t)$ is the optimal just threshold cathodic shape for minimum energy dissipation, the anodic shape $i_a(t)$ should minimize energy dissipation while verifying:

$$\int_0^{t_c} i_{c,T}(t).dt + \int_{t_c+t_d}^{t_c+t_d+t_a} i_a(t).dt = 0 \qquad (23)$$

Let us assume that $q_{e,c}(t)$, given by (18), takes the threshold value $q_{e,T}$ for $t = t_c + \varepsilon_c$ In this case, applying Cauchy-Buniakowski-Schwartz (CBS) inequality ([12]), we have:

$$q^2{}_{e,T} = \left| \int_0^{t_c} G(t_c + \varepsilon_c - u).i_c(u).du \right|^2 \le \left(\int_{\varepsilon_c}^{t_c+\varepsilon_c} G^2(u).du\right)\left(\int_0^{t_c} i^2{}_c(u).du\right) \qquad (24)$$

The minimum of dissipated energy is attained when the inequality becomes equality, and this happens for $0 \le t \le t_c$ if and only if:

$$i_c(t) = i_{c,T}(t) = K_c G(t_c + \varepsilon_c - t) \qquad (25)$$

The proportionality constant is calculated substituting (25) in the just threshold condition: $q_{e,c}(t_c + \varepsilon_c) = q_{e,T}$

We obtain:

$$K_c = \frac{q_{e,T}}{\int_{\varepsilon_c}^{t_c+\varepsilon_c} G^2(u).du} \qquad (26)$$

Now, once $i_{c,T}(t)$ is determined, $Q_a = \int_{t_c+t_d}^{t_c+t_d+t_a} i_a(t).dt$ is fixed by (23).

But if $1(t)=1$ for every t, then applying a second time CBS inequality:

$$\left| \int_{t_c+t_d}^{t_c+t_d+t_a} 1(t).i_a(t).dt \right|^2 \leq t_a. \int_{t_c+t_d}^{t_c+t_d+t_a} i^2{}_a(t).dt$$

This can be equality, and the energy dissipated in the tissues during the anodic phase is a minimum, if and only if the anodic pulse is *a rectangular one*:

$$i_a(t) = K_a.\{H(t-(t_c+t_d)) - H(t-(t_c+t_d+t_a))\} \qquad (27)$$

The restriction (23) gives:

$$K_a = \frac{Q_a}{t_a} \qquad (28)$$

Thus, given the impulsive response function of the electrode-tissues-target element system, the durations of the cathodic and anodic phases, and a suitable lower bound for the interval of time between these phases, the shape of the *just threshold biphasic pulse* that minimizes the energy dissipated in the tissues was derived from the excitation functional and the well-known CBS inequality.

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